Preventing Toxic Side Effects of Inflammatory Disease Therapy

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Researchers at the University of California, San Diego (UCSD) School of Medicine have developed a mouse model that could help scientists develop better drugs to fight autoimmune and inflammatory disorders such as multiple sclerosis and rheumatoid arthritis.

Inflammation is a process by which the white blood cells and chemicals of the immune system rally to protect the body from infection and foreign substances such as bacteria and viruses. In autoimmune diseases, however, this defense system triggers an inflammatory response when there are no foreign substances to fight off, or the defense system goes into "overdrive" and forgets how to turn off. In these diseases, the body's normally protective immune system attacks and damages its own healthy tissues.

UCSD researcher Mark H. Ginsberg, M.D., professor of Medicine at the University of California, San Diego (UCSD) School of Medicine, and his colleagues have identified a mechanism to selectively disrupt signaling to recruit lymphocytes and monocytes – white blood cells sent to sites of inflammation to fight infection – while maintaining the body's other essential immune system functions. Their findings appear online on February 9 in advance of print publication in the March issue of the *Journal of Clinical Investigation*.

In the case of certain autoimmune diseases, the alpha 4 integrins cause white blood cells to accumulate at the site of the disease, resulting in inflammation. An integrin is a surface molecule found on the exterior of cells that helps cells adhere and migrate. It is also believed to be responsible for a role in cell signaling, which allows cells to communicate with the extracellular environment. One of the promising treatments for disorders such as multiple sclerosis, inflammatory bowel disease and rheumatoid arthritis – the alpha 4 integrin antagonist – works by blocking cell adhesion. However, this anti-inflammatory therapy could cause adverse side effects, such as impairment of the immune system and the patient's ability to develop new red and white blood cells in the bone marrow, a process called hematopoiesis.

"Our goal was to identify a more specific target of alpha 4 integrin molecules in order to interfere with their roles in disease progression while sparing alpha 4 functions required for normal health," said David M. Rose, D.V.M., Ph.D., assistant professor of medicine at UCSD, and co-author of the study.

The research team created mutant mice known as "alpha4(Y991A) mice," in which the alpha 4 integrin can no longer bind to a signaling protein inside the cell called paxillin. Previously generated alpha 4 integrin deficient mutant mice died at birth because too many aspects of alpha4 function were changed. The new alpha4(Y991A) mice have an impairment only in the interaction between alpha4 and paxillin, and thus have fewer effects on development. The researchers discovered that, in contrast to normal mice, alpha4(Y991A) mice exposed to an inflammatory stimulus recruited fewer circulating white blood cells (B and T cells) to the region of exposure. However, the development of new B and T cells was unaffected.

The authors suggest that these mice are a valuable tool to test models of inflammatory and autoimmune diseases of humans, and that a new class of pharmaceutical agents that target the specific interaction of paxillin and alpha 4 integrin could be important future treatments of inflammatory disease.

"We were surprised to find that the mutation actually had very little effect on the animal's development of lymphocytes, the white blood cells that fight infection," said Rose. "This could prove to be an important first step in development of a more effective drug to target alpha 4 integrins in autoimmune and inflammatory disease of humans."

Additional co-authors include Kenneth Kaushansky, M.D., Chloé C. Féral, Jaewon Han, Norman Fox and Gregg J. Silverman, UCSD Department of Medicine.

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